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Clinical and mutational characteristics of Duchenne muscular dystrophy patients based on a comprehensive database in South China

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Abstract

The development of clinical trials for Duchenne muscular dystrophy (DMD) in China faces many challenges due to limited information about epidemiological data, natural history and clinical management. To provide these detailed data, we developed a comprehensive database based on registered DMD patients from South China and analysed their clinical and mutational characteristics. The database included DMD registrants confirmed by clinical presentation, family history, genetic detection, prognostic outcome, and/or muscle biopsy. Clinical data were collected by a registry form. Mutations of *dystrophin* were detected by multiplex ligation-dependent probe amplification (MLPA) and Sanger sequencing. Currently, 132 DMD patients from 128 families in South China have been registered, and 91.7% of them were below 10 years old. In mutational detection, large deletions were the most frequent type (57.8%), followed by small deletion/insertion mutations (14.1%), nonsense mutations (13.3%), large duplications (10.9%), and splice site mutations (3.1%). Clinical analysis revealed that most patients reported initial symptoms between 1 and 3 years of age, but the diagnostic age was more frequently between 6 and 8 years. 81.4% of patients were ambulatory. Baseline cardiac assessments at diagnosis were conducted in 39.4% and 29.5% of patients by echocardiograms and electrocardiograms, respectively. Only 22.7% of registrants performed baseline respiratory assessments. A small numbers of patients (20.5%) were treated with glucocorticoids. 13.3% of patients were eligible for stop codon read-through therapy, and 48.4% of patients would potentially benefit from exon skipping. The top five exon skips applicable to the largest group of registrants were skipping of exons 51 (14.8% of total mutations), 53 (12.5%), 45 (7.0%), 55 (4.7%), and 44 (3.9%). In conclusion, our database provided information on the natural history, diagnosis and management status of DMD in South China, as well as potential molecular therapies suitable for these patients. This comprehensive database will promote future experimental therapies in China.

Keywords: Duchenne muscular dystrophy; Database; Natural history; Patient management; Dystrophin gene

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder. As the most frequent muscular dystrophy in children, the estimated prevalence of DMD is approximately 1 in 3500 newborn males [1]. DMD patients present with progressive proximal weakness and commonly lose the independent ambulation before the age of 13. Heart failure and respiratory complications appear with age and become the most common causes of death in DMD patients around the second or third decade. The devastating natural history of DMD is caused by mutation of the *dystrophin* gene, leading to disruption and premature termination of the translational reading frame, which results in a deficiency of the protein dystrophin. Mutations that respect reading frame in the *dystrophin* gene cause a milder muscular dystrophy known as Becker muscular dystrophy (BMD) [2]. Many different types of mutations for DMD have been reported, including large deletions, large duplications, and small mutations [3].

Current recommended management strategies for DMD, including corticosteroid treatment, surgical management, cardiac and respiratory intervention, have improved muscle

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function, survival and quality of life [4,5]. This reflects the fact that the natural history of DMD has been changed by these effective measures. Despite these advances, the progression and disastrous outcome of the disease cannot be modified. Potential therapeutic approaches that target the causative genetic mutations raise hopes of promising treatment for DMD. The exon skipping approach restores the open reading frame of dystrophin transcripts with antisense oligonucleotides, leading to the restoration of truncated but partly functional dystrophin protein in subgroups of DMD patients with specific frameshift mutations [6]. Nonsense stop codon read-through therapy induces ribosomal read-through of premature stop codons and could potentially benefit for DMD patients with nonsense mutations [7].

Many clinical trials of molecular genetic therapies have been planned and conducted for DMD [8]. In China, even though mutational characteristics of Chinese DMD/BMD patients have been described in several studies [9–11], the development of experimental therapies faces many challenges due to the lack of epidemiological data, the natural history of the disease and information about clinical care. Thus, a comprehensive database that provides these detailed data is crucial not only for genetic diagnosis and consulting but also for basic scientific research and potentially guidance of future clinical trials. To date, only one comprehensive database for DMD in East China from a single centre has been reported [12]. However, the data from other areas of China are still limited. Therefore, we developed a registry database on the base of DMD patients from South China to analyse the clinical and molecular genetic characteristics of DMD patients in this area. Through comprehensive analysis, we aimed to provide detailed information about the natural history, clinical diagnosis and management status of DMD in South China, as well as potential molecular therapy strategies suitable for DMD patients.

2. Materials and methods

2.1. Patients

The database included male DMD patients from South China. All the registered patients attended the neuromuscular clinic at the First Affiliated Hospital of Fujian Medical University for regular visits from February 2013 to May 2016. Every included patient had suspected clinical symptoms related to DMD (progressive proximal weakness present by 8 years of age, positive Gowers' sign, calf pseudohypertrophy, significantly elevated creatine kinase (CK) level), and the diagnosis of DMD was confirmed by at least one of the following criteria: (1) a muscle biopsy demonstrating complete dystrophin deficiency; (2) a positive large deletion or duplication (≥1 exon) in *dystrophin* that was expected to shift the reading frame and produce premature termination of dystrophin protein; (3) complete *dystrophin* gene sequencing showing a small mutation, including nonsense mutations, small insertions or deletions, that was predicted to disrupt the reading frame and preclude synthesis of dystrophin protein; and (4) patients with in-frame mutations, splice site mutations or missense mutations were further confirmed by the results of muscle biopsy or the positive outcome of patients or their siblings losing ambulation before the age of 13 years (Fig. 1). Registration for the database is voluntary. Information about the content and aim of the registry

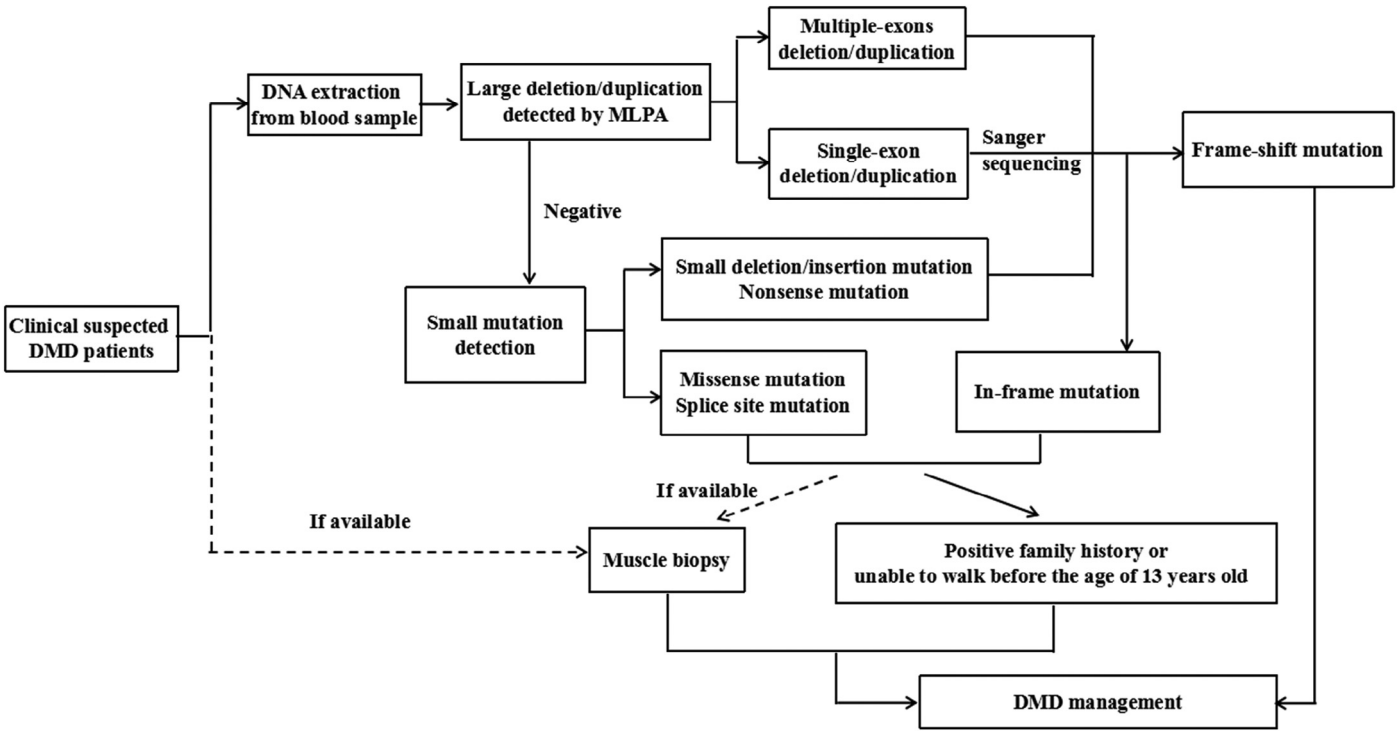

Fig. 1. The diagnostic flowchart for Duchenne muscular dystrophy in the database.